



Official journal of the Pan African Urological Surgeon's Association
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Uro-oncology

Case report

Giant angiomyolipoma in a tuberous sclerosis patient and review of the literature



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Received 26 January 2018; received in revised form 11 May 2018; accepted 3 June 2018; Available online 11 August 2018

KEYWORDS

Renal angiomyolipoma;
Giant renal
angiomyolipoma;
Tuberous sclerosis
complex;
Nephrectomy;
Mammalian target of
rapamycin

Abstract

Introduction: About 20% of renal angiomyolipomas (RAML) are associated with tuberous sclerosis complex (TS). About 34–80% of patients with TS present with RAML. RAMLs associated with TS are at higher risk of potentially life-threatening hemorrhage and hypovolemic shock. Only a few case reports of giant RAML, defined as larger than 10 cm in diameter, and its management, have been reported.

Observation: We present a 21 year old woman with abdominal distension over the last 2 years. A contrast-enhanced CT scan revealed a giant RAML on the left side. Based on the presence of at least 3 major features of the clinical diagnostic criteria of tuberous sclerosis complex, the diagnosis was made. An open nephrectomy was performed. Therapeutic options described in literature are conservative management, medical treatment with mTOR inhibitors, arterial embolization, radioablation and partial or total nephrectomy.

Conclusion: In giant TS-associated RAML total nephrectomy, rather than conservative treatment, is the treatment of choice in order to reduce the risk of potentially life-threatening bleeding.

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Introduction

Renal angiomyolipomas (RAML) are rare, benign tumors consisting of vascular elements, smooth muscle and adipose tissue. About

20% of them occur in patients with the tuberous sclerosis complex (TSC) [1–3]. In the presence of bilateral lesions, one should consider a diagnosis of this neurocutaneous condition that also causes benign tumors in the brain, heart, eyes, lung and skin [1]. Smaller RAMLs are often incidentally found on radiological examination, whereas RAMLs larger than 4 cm are at higher risk of bleeding [1,3]. RAML associated with TS are more likely to lead to potentially life-threatening retroperitoneal hemorrhage due to their size, and multifocal and bilateral nature [1–3]. Embolization, partial or total nephrectomy as treatment of larger RAMLs have

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Peer review under responsibility of Pan African Urological Surgeons' Association.

<https://doi.org/10.1016/j.afju.2018.06.003>

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Figure 1 A. Facial angiofibromas. B. Hypomelanotic macule on the left chest >5 mm.

been described [3]. Only a few case reports about giant RAML, which is defined as larger than 10 cm in diameter, and its management, have been published [4]. We present a case of giant RAML in a young woman who presented with left abdominal pain and in whom the diagnosis of tuberous sclerosis was made.

Case presentation

A 21 year old woman was referred to the urology department of Groote Schuur Hospital in Cape Town (South Africa) in November 2017 because of weight loss and progressive abdominal distension over the last two years. No relevant medical or family history was reported. An ultrasound of the kidneys which was done at the referring hospital reported a big solid mass on the left side of the abdomen.

Skin inspection showed multiple (>10) facial angiofibromas and 4 hypopigmented macules on the chest, lower back and right buttock (Fig. 1). Multiple skin lesions with a 'confetti' appearance were seen on both arms and legs. No other dermatologic or dental features of TS were seen. Inspection of the abdomen showed abdominal distension on the left side. A large non-tender mass was palpated in the left upper quadrant extending beyond the midline.

Laboratory results showed anemia (Hb of 9,4 g/dl) and microscopic hematuria. A contrast enhanced CT-scan of the abdomen revealed a heterogeneous left renal mass with areas of soft tissue and fat components (Hounsfield units of $-68,97$), measuring $123,0 \times 159,4$ mm (Fig. 2). The right kidney showed multiple cortical hypodensities with the largest measuring 11 mm. Both lesions were reported as suspicious for angiomyolipoma (AML).

Blood transfusion with 2 units of packed cells was given. A left radical nephrectomy was performed through a chevron incision under general anesthesia. A mass with a diameter of $290 \text{ mm} \times 215 \text{ mm} \times 120 \text{ mm}$ and a weight of 3,58 kg was removed (Fig. 3). The procedure was complicated intraoperatively by pancreatic tail injury requiring distal pancreatectomy. She developed a pancreatic leak which required a stay in the Intensive Care Unit. The leak resolved spontaneously. The patient was discharged 3 weeks after surgery.



Figure 2 Axial image from a contrast enhanced computed tomography (CT) shows a primarily fat containing mass arising from the left kidney suggestive of a giant angiomyolipoma (Hounsfield units of $-68,97$).



Figure 3 Excised tumor of 3,58 kg, showing a mixture of mature adipose tissue and thick walled blood vessels.

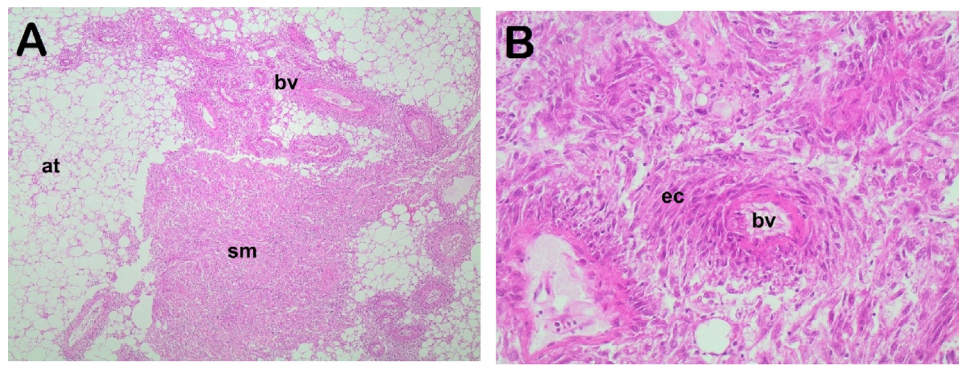


Figure 4 A. Histopathological examination demonstrated smooth muscle, mature adipose tissue and thick walled blood vessels (hematoxylin and eosin stain, magnification $\times 40$). B. Epithelioid smooth muscle cells emanating from blood vessel walls (haematoxylin and eosin stain, magnification $\times 200$).

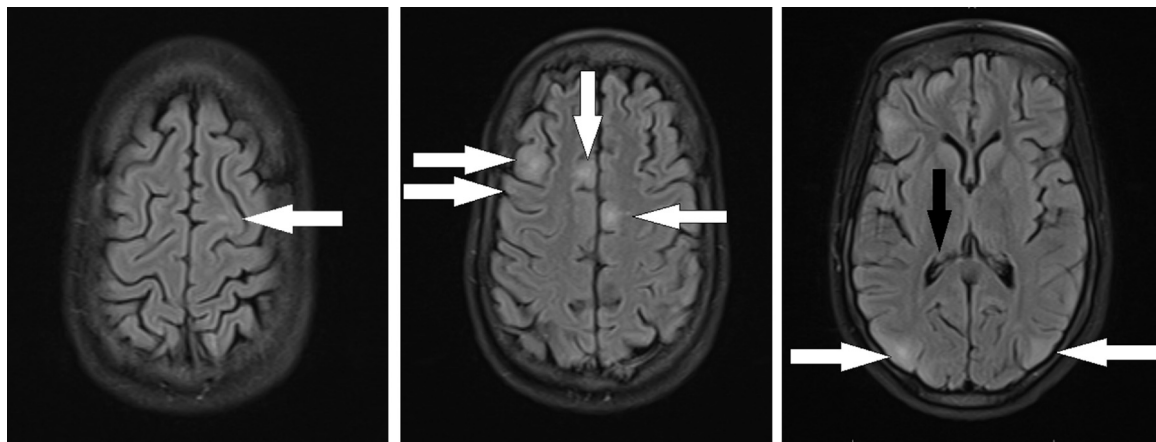


Figure 5 Axial Magnetic resonance imaging (MRI) (T2 weighted) of the brain, demonstrating white matter hyperintensities and right ventricular small subependymal nodule (indicated by white arrows and black arrows, respectively).

Histopathology of the mass confirmed an angiomyolipoma consisting of a combination of spindled smooth muscle cells, mature adipose tissue and thick walled blood vessels. Smooth muscle cells which emanated from the walls of the blood vessels frequently had an epithelioid morphology (Fig. 4). A few of the many lymph nodes submitted contained a combination of both smooth muscle and adipose tissue components of angiomyolipoma. Immunohistochemical staining was not required.

Further investigation with MRI brain showed multiple cortical and subcortical T2 weighted white matter hyperintensities and multiple predominantly right ventricular small subependymal nodules. No subependymal giant cell astrocytoma was seen (Fig. 5). Expectative management was performed since neurological investigation was negative for mental retardation or epilepsy.

Ophthalmologic consult revealed no lesions indicative of a retinal hamartoma. Electrocardiogram did not show any cardiac arrhythmias therefore, echocardiography was not performed. Genetic screening unfortunately could not be done due to non-availability of the service.

According to the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus (ITSCC) our patient meets 4

major criteria to confirm the diagnosis of TSC: >2 angiomyolipomas, >3 facial angiofibromas, 4 hypopigmented macules (>5 mm diameter) and subependymal nodules in the brain [5] (Table 1).

Discussion

TS is an autosomal dominant disease, most often caused by a mutation of the *TSC1* or *TSC2* gene, with incomplete penetrance, which affects multiple organ systems. Prevalence in the literature varies from 1/6000 to 1/12000 individuals [1,6–8]. About 34–80% of patients with TS present with renal angiomyolipoma (RAML) and about 20–30% of RAML cases are associated with TS [9]. RAML associated with TS typically manifest at a younger age, are bilateral and multifocal, grow with time, and are more likely to lead to potentially lifethreatening hemorrhage [10]. Giant RAMLs are defined as larger than 10 cm in diameter [4]. Very little literature is written about giant RAMLs. Our patient presented with abdominal distension for 2 years, and pain in the abdomen and back for 3 months, without signs of hypovolemic shock. She did not have any urinary symptoms. Patients with TS-associated giant RAMLs as reported by Lin et al., Katz et al. and Tsutsumi et al. presented with cyclic left flank pain, general fatigue, and epigastric fullness [2,11,12]. About 10% of patients with RAML present with acute flank pain, haematuria, and signs of internal bleeding which is char-

Table 1 Clinical diagnostic criteria of TSC.

Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

Major features

1. Hypomelanotic macules (≥ 3 , at least 5-mm diameter)
2. Angiofibromas (≥ 3) or fibrous cephalic plaque
3. Ungual fibromas (≥ 2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangiomyomatosis (LAM)†
11. Angiomyolipomas (≥ 2)‡

Minor features

1. “Confetti” skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥ 2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥ 2 minor features

acteristic of ‘Wunderlich Syndrome’; a urological emergency of retroperitoneal hemorrhage which manifests as hypovolemic shock. The presence of intratumoral aneurysms >5 mm in tumors >4 cm has also been reported as a risk factor for spontaneous retroperitoneal hemorrhage [13].

Treatment options for RAML described in the literature include active surveillance with reimaging, partial/total/radical nephrectomy, radiofrequency- or cryoablation and selective mTOR inhibitors such as everolimus.

In general, indications for intervention for renal AML are the presence of symptoms, high risk of bleeding and size (>4 cm), even when asymptomatic [14]. However, the indication of tumor size has been questioned recently. Kuusk et al. showed that only tumors >6 cm are at a higher risk for bleeding while Chronopoulos et al. showed that even tumors <8 cm tend to be asymptomatic [4,15].

Active surveillance seems to be appropriate for tumors smaller than 4 cm only [16,17]. On the contrary, Ouzaid et al. stated that active surveillance can also be an option in tumors >4 cm. They suggest that the historically quoted threshold of 4 cm may lead to overtreatment [18].

However, it must be noticed that the above studies included both sporadic and TS associated RAML. Hence, larger lesions are at higher risk of bleeding, but there is no consensus on what size should be used as the cutoff for intervention. In this case, treatment indication was clear, since the patient had a symptomatic giant RAML (290 mm \times 215 mm \times 120 mm). Surgical treatment seems to be the treatment of choice in larger RAML, if renal malignancy is suspected or in cases of hemorrhage [19]. Since RAML in TS is often bilateral and multifocal, and is known to have a higher recurrence rate, nephron sparing surgery (NSS) is highly recommended either by selective embolization or partial nephrectomy [15,16,20]. Selec-

tive arterial embolization (SAE) is now a first-line treatment option in RAML and particularly used in cases of acute hemorrhage and hemodynamic shock [20]. Compared to surgical treatment, the most important advantage is sparing of the renal parenchyma and the minimally invasive nature of the procedure. However, recurrence rates after SAE in TS associated RAML vary from 11 to 40%, hence continuous follow-up is required [21]. Moreover, in this case selective embolization was technically impossible since the AML substituted the majority of the parenchyma of the left kidney. The same technical impossibility applies for a partial nephrectomy.

The most recently introduced treatment option in RAML is targeted therapy which inhibits the mammalian target of rapamycin (mTOR). The aim of the treatment is to reduce tumor progression and promote regression of existing tumor. According to recent literature mTOR inhibitors are effective and safe in regulating asymptomatic TS associated RAML >3 cm not amenable to other treatment. Additionally, renal parenchyma will be spared in this treatment [22]. However, Cabrera-Lopez et al. suggest that the effect of mTOR inhibitors is unlikely to be durable [23]. Moreover, everolimus for example is associated with stomatitis (48%), nasopharyngitis (24%), acne-like skin lesions (22%), headache (22%), cough (20%) and hypercholesterolemia (20%). Long-term consequences of mTOR toxicity remain unknown [22]. Since our patient had a symptomatic TS associated RAML >3 cm, treatment with mTOR inhibitors was not appropriate in this case. However, this patient had asymptomatic smaller lesions (biggest lesion was 11 mm) in the other kidney as well. At this stage treatment with mTOR inhibitors for the right kidney is premature since the lesions are <3 cm. mTOR inhibitors can be considered when lesions are >3 cm. We will see the patient at our outpatient clinic in 6 months for follow-up, with a CT scan in advance.

Specific research on treatment options for giant RAML has not been reported so far. Owing to the size of the tumor in giant TS-associated RAML we assume mTOR inhibitors might potentially play a role in their management, alongside surgical treatment.

Conclusion

The present case report highlights two important aspects for clinicians. First, in giant TS-associated RAML, partial or total nephrectomy, rather than conservative treatment, is the treatment of choice in order to reduce the risk of a potentially life-threatening bleed. However, in this case report we would like to emphasize the technical challenge of nephron sparing treatment in giant RAML. Second, future research is needed to further explore the role of mTOR inhibitors in the treatment of giant RAML.

Conflict of interest

We have no conflict of interest to declare.

Authors' contributions

Jolien Mensink: clinical examination of patient, collection of data, literature review, writing of introduction, case presentation, discussion and conclusion.

Michael Locketz: selection of histopathology images, comment on images, review of grammar and spelling of case report.

John Lazarus: head of department, coordinator and main reviewer of case report.

Consent from the patient

A written consent from the patient was obtained.

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